Bandolier 18

What do we think?
What do we know?
What can we prove?

Evidence-based health care

First published August 1995

THE NEW GENETICS - CONSEQUENCES FOR CLINICAL PRACTICE

The rapid progress now being made in molecular genetics will have far reaching consequences for clinical practice. It will be crowned by the completion of the largest co-operative international biomedical project ever undertaken: the mapping and sequencing of the human genome. This will not only radically increase our understanding of normal development and disease processes but it will also open up possibilities for new methods of preventing, diagnosing and treating currently intractable diseases. Not surprisingly this new and powerful knowledge will bring with it, indeed, it has already posed new and difficult ethical, social and economic problems.

The R&D Directorate has commissioned two reports on the likely implications for the NHS of this rapid progress in genetics and the associated technology. They are due to be published soon.

Bandolier will discuss some of these new areas of genetics in simple terms in an occasional Gene Watch series, highlighting the progress and opportunities provided but also posing some of the questions that the NHS and society at large must face. We would welcome readers' comments on what they would find most useful and interesting.

This issue starts with a brief consideration of breast cancer genetics and the significance of the recent identification of the inherited susceptibility gene BRCA1.

GENETICS OF BREAST CANCER

The present management of breast cancer in the UK provides a classic case of the opportunities and dilemmas presented by the new genetics. Up to 10% of the 25,000 new breast cancer patients each year have an inherited basis. Young age at onset and strong family history are the most obvious indicators. The implication is that more than 1,000 women per year will join the ranks of those at very high risk of getting breast cancer (a lifetime risk of over 80%).

Susceptibility genes BRCA1& BRCA2

Paul Broca in 1866 is reputed to be the first person to report the importance of family history in breast cancer. Warthin in 1913 reported the results of the first comprehensive study of family histories in cancer. But it was not until 1990 that Marie-Clare King reported mapping, by segregation analysis, the first breast cancer susceptibility gene (BRCA1) to chromosome 17q21. The recent identification and sequencing of the gene by Mark Scolnick and colleagues in the USA has ended the race by at least 8 major scientific groups around the world to be the first team to isolate the gene - the fact that there are 46 authors is itself a comment on modern research.

The BRCA1 gene confers an 83% risk of breast and 63% risk of ovarian cancer by age 70 and a modestly elevated risk of colon and prostate cancer.

A second breast cancer susceptibility gene, BRCA2, has recently been mapped to chromosome 13q12. This gene probably confers about the same risk of early onset (female) breast cancer as BRCA1 but it also appears to increase the risk for male breast cancer and be less involved in ovarian cancer. A third, as yet unmapped, locus is thought to confer up to 1/5 of the total inherited risk.

Other 'breast cancer' genes

Breast cancer also occurs as a part of the rare Li-Fraumeni syndrome which is usually associated with germline mutations of the p53 gene located on chromosome 17p12. The AT (Ataxia Telangectasia) gene on chromosome 11q22 is also thought to play an important role in breast cancer, claims being made that it may be responsible for up to 13% of cases.

Several oncogenes and tumour supressor genes have been implicated in ***sporadic*** (i.e. non- inherited) cases of breast cancer. Those most commonly implicated in such sporadic breast cancers are p 53 on chromosome 17p12; rb on 13q14; AT on 11q22; cmyc on 8q24; cerbB2 on 17q; and int2, hst1, prad1 and ems1 all on 11q13. Mutations in these genes in somatic cells underlie the malignant transformations leading to these tumours.

Tests and screening

Any investigations or screening tests based on these genes will be fundamentally different from genetic tests for the susceptibility genes BRCA 1 and 2. Although they may be valuable in establishing an accurate diagnosis, helping to clarify the prognosis and suggesting the most appropriate therapy they will have consequences ***only*** for the patient in which they are found and not in any of the patient's relatives. Professor Bruce Ponder has offered guidelines to GPs on which relatives of breast cancer patients should be referred to specialist clinics for counselling and screening.

The recent isolation and sequencing of the BRCA1 gene provides the basis for a DNA test of susceptibility for high risk women but there is almost universal agreement that this would be premature outside a strictly controlled research programme. It does, however, emphasise the urgency of the situation and the need to agree a coherent screening policy perhaps involving regulation or licensing of testing.

If this is not done market forces will predominate and it will then be very difficult to introduce a rational, controlled and cost-effective programme.

Unfortunately the situation regarding the gene test is more complex than might have been hoped. At least 100 different mutations have already been identified in the BRAC1 gene and it is likely that many more will found. Information on the frequency and severity of effect of these different mutations will be needed and the sensitivity and specificity of any proposed diagnostic test must be established before it is adopted as a routine procedure.

Questions to be answered

When an acceptable test becomes available a number of difficult questions will need to be answered:-

- Who will decide whom to test?
- How many of the female relatives of existing breast cancer patients should be offered the gene test and counselling?
- Who else should be eligible for testing?
- What advice should be offered to individuals found to have BRCA1 mutations?

Options after a positive test

- Bilateral mastectomy, but if this option is chosen then logically removal of the ovaries should also be considered? When should surgery be done?
- Prophylactic tamoxifen, or other anti-oestrogen treatment (trials of effectiveness are currently in progress but results not yet known). From what age and for how long should prophylaxis be continued?
- Intensive surveillance including mammography, but the effectiveness of this in patients below 50 is still disputed and it may be positively harmful in a subset of patients who are more sensitive than normal to the effects of radiation.
- What advice should be offered to individuals found ***not*** to have BRCA1 mutations? Should their surveillance be different from the normal population with its 1 in 12 lifetime chance of breast cancer?

All this highlights the urgent need for carefully planned programmes to evaluate these options. ***Bandolier*** will try to highlight evidence-based information as it becomes available.

Dr Eric Sidebottom, Oxford

WHICH GRADUATED COMPRESSION STOCKING?

One of the successes of consumers' associations in the UK and elsewhere has been to draw attention to the very real differences that exist in the performance and quality of products. To a large extent publications like "*Which?*" introduced the concept of evidence-based purchasing to everyday life. It has been very successful - and perhaps one of the main reasons why cars, for instance, do not now rust through in just a few years.

There are probably examples in health care - but they are not always so obvious, which just increases the pleasure when one appears.

Report

Stephen Thomas of the Surgical Materials Testing Laboratory at Bridgend General Hospital has sent ***Bandolier*** a copy of a report produced in 1992 on graduated compression stockings. It makes gripping reading.

The report contains a comparison of the compression profiles produced by 10 brands of elasticated stockings intended for the prevention of deep vein thrombosis (DVT) in non-ambulant patients. While there was not, in 1992, a formal specification for compression stockings in bedridden patients the principles of some appropriate British Standards were applied.

British standard leg

There are five 'standard legs'. Thigh-length stockings were tested using sizes appropriate to each of the standard legs, again using appropriate British Standard methods, before and after washing by British Standard methods. The average pressures exerted at the ankle, calf, knee and upper and lower thigh positions were compared with values recommended in the literature.

Recommendations

In order to exert an optimal clinical effect a stocking designed to prevent an embolic event in a patient confined to bed should meet the following design and performance criteria:-

- Produce graduated compression decreasing from ankle to knee
- Calf pressure should be about 15 mmHg
- All sizes should produce consistent compression profiles in appropriate sized legs
- There should be no tourniquet effect at the top
- Available in a large range of sizes
- There should be little variation in pressure produced when applied to legs slightly different from "standard"
- Pressures produced should remain unaffected by washing
- Minimum information should be printed on the stocking

Results

None of the stockings tested in 1992 met all of these conditions. Two brands were closest. They were TX (from Brevet) and Thrombex (from Seton). The performance of others varied, but several performed so badly that the were considered of questionable value or even potentially hazardous in some circumstances.

Literature review

The report comes with a very useful and thorough literature review and history of the development of graduated compression stockings. It is an exemplar of what we need to see to make evidence-based purchasing effective in the NHS.

Reference:

S Thomas. Graduated external compression and the prevention of deep vein thrombosis. 1992 ISBN 1 874517 00 2.
Dr S Thomas, SMTL, Bridgend General Hospital, Quarella Road, Bridgend, Mid-Glamorgan CF31 1JP. Tel: 01656 652166.

ALTERNATIVES

Alternative therapies play an important part in the lives of some individuals. Many people put their trust in some aspects of these - but what is the evidence for their effectiveness?

A useful book which brings together a number of systematic reviews of alternative medical therapies [1] examines the evidence for effectiveness of alternative diagnosis (iridology), acupuncture, homeopathy, vitamin supplementation and plant products. Though from the excellent group with Paul Knipschild in Maastricht, the only problem for many will be that about 60% of the book is in Dutch.

Ginko

One of the most interesting positive findings in the book is the evidence based on reviews of over 40 clinical trials that one alternative therapy, ginko extracts, are effective.

Extracts from the leaves of Ginko biloba have been used therapeutically for centuries, especially in traditional Chinese medicine. Extracts of leaves and other parts of the tree can be made into tea. Extracts can be partially purified and dried, and a number of ginko preparations are used widely in some European countries.

The extracts contain a number of complex organic molecules, including a family of ginkolides. These are know to be platelet-activating factor antagonists (PAF-antagonists), a group of substances with an interesting chemistry and some fascinating therapeutic potential in a range of clinical conditions with effects on the nervous system, inflammatory disorders and reproduction [2,3].

The main indications for ginko are peripheral vascular disease such as intermittent claudication and "cerebellar insufficiency". This latter is an imprecise term that describes a collection of symptoms, especially in elderly people:-

Difficulties of concentration and memory
Absentmindedness
Confusion
Lack of energy
Tiredness
Decreased physical performance
Depressive mood
Anxiety
Dizziness
Tinnitus
Headache

These are associated with impaired cerebral circulation.

Systematic review

Forty clinical trials were found for ginko extract used in cerebral insufficiency, of which eight were high quality [4]. The results were homogeneous - virtually all produced positive results for ginko extract taken at about 120 mg a day for 4 - 6 weeks. Adverse effects are reported as rare.

Details of the results of ginko extracts in the eight quality trials in cerebral insufficiency and the two good studies in intermittent claudication have also been given [5].

Comment

These reviews have concentrated on the methodological quality of the studies, and have abstracted a number of high quality studies which predominantly favour ginko extracts over placebo for the outcomes chosen. The magnitude of the increased effects is often quite large.

It is slightly frustrating that the potential impact of ginko as a treatment or dietary supplement does not come over. It may be quite important. Given that it appears safe, positive effects on some of the symptoms of "cerebral insufficiency" in the growing number of elderly people in Britain could have profound benefits.

References:

1 J Kleijnen, G ter Riet, P Knipschild. Effectiviteit van alternatieve geneeswijzen: Ein literatuuronderzoek. Rijkuniversiteit Limburg 1993. ISBN 90-74130-09-7.
2 M Koltai, D Hosford, P Guinot, A Esanu, P Braquet. Platelet activating factor (PAF). A review of its effects, antagonists and possible future clinical implications (Part I). Drugs 1991 42: 9-29.
3 M Koltai, D Hosford, P Guinot, A Esanu, P Braquet. PAF. A review of its effects, antagonists and possible future clinical implications (Part II). Drugs 1991 42: 174-204.
4 J Kleijnen, P Knipschild. Ginko biloba for cerebral insufficiency. British Journal of Clinical Pharmacology 1992 34: 352-8.
5 J Kleijnen, P Knipschild. Ginko biloba. Lancet 1992 ii: 1136-9.

ECONOMICS AND HEALTH CARE

Have you ever wanted to have a description of health economics that made some sort of sense to you? ***Bandolier*** has found a sensible description that is really helpful to people trying to get their brains around how *clinical* effectiveness and *economic* effectiveness can be brought together.

It comes from the Cochrane Collaboration handbook - and we found it on-line on the Internet, though it is also found in the printed version [1]. It is designed to help reviewers and economists to work together.

Making decisions

Decisions about health care often entail making trade-offs between the estimated benefits and the estimated harms and costs of the intervention. This can occur if the benefits and costs are both either higher or lower for one form of health care than for another.

Resources will always be limited. They should be used to provide equitably those forms of health care that have been shown in properly designed evaluations to be effective. The need for efficiency in health care, and other activities, arises from the fact that there will never be enough resources to satisfy human wants completely.

Scarcity

Given this notion of *scarcity*, if follows that use of resources for a given form of health care inevitably involves a sacrifice. That is, the health care system forgoes the opportunity to use the same resources in other beneficial activities. Consequently the economist measures *cost* in terms of the benefit that would be derived from using resources in their best alternative use.

Hence the economist's term, *opportunity cost*. This concept should be contrasted with a strictly financial concept of cost, which relates to the cash outlays for units of the resource. It is important for reviewers to bear in mind this important distinction when considering what data to collect about cost from trials. While economic and financial estimates of cost will sometimes coincide, this is frequently not the case.

Cost effectiveness

The *cost-effectiveness* of a particular form of health care can be defined as the ratio of the net change in health care costs to the net change in health outcomes. Following these definitions of cost and cost-effectiveness, it is possible to state what information economists require in order to perform cost-effectiveness analyses or other types of economic evaluations:

- identification of all main event pathways that have distinct resource implications or outcome values associated with them
- estimation of the probabilities associated with the main event pathways
- descriptive data to enable the resource consequences associated with each pathway to be measured
- descriptive data to enable the outcomes associated with each pathway to be valued

Event pathways

Event pathways represent substantively different health outcomes or processes. They consist of a clinical event, how that event is managed, the resources used to manage that event, subsequent events associated with either the event or how it is managed, and the cost of those resources.

Doing-it-yourself

These pages in the Cochrane handbook go on to give a straightforward account of how reviewers or others can construct simple clinical event pathways to enable them to perform an economic evaluation. It indicates which are the important events to be identified and the time scales to be examined, especially in follow up.

Great practical information, readable, and above all interesting. The main feature that shines through is that the economic analysis follows the clinical event - which is the way it should be.

Reference:

Preparing and maintaining systematic reviews (editor Andy Oxman). The Cochrane Collaboration handbook, 1994 VI 43-49.
Also on the Internet at:
http://hiru.mcmaster.ca/cochrane/default.htm

Costing drug treatments

Bandolier 15 contained a letter about costs of drug treatments. The implication was that it would be most cost effective to treat urinary infections with trimethoprim (about 76% effective with a cost of £0.38 per patient) as a first line with the more costly but more effective drug cephalexin (about 95% effective, £3.60 per patient) reserved for those who fail to respond. The thesis was that in a study of over 4,000 patients with UTI from Epsom & Ewell about £8,000 a year could be saved using such a scheme.

Costing GPs time

Professor John Mellerio of London and Dr David Jenkins, a GP from Cardiff, take a different view. They argue that a major cost that should be included is the time taken by the GP in seeing the 19% of patients who had not responded to trimethoprim. In money terms this would involve seeing about 800 patients again, for about 10 minutes each. This is about 130 hours of GPs' time a year, which, if costed at the BMA rate of £100 an hour amounts to about £13,000 and would have to be added to the costs of using trimethoprim as first line treatment.

Using this argument, they say, the use of cephalexin as a first treatment would be the most cost-effective. How, in addition, should the costs of the 4,000 or so days of continued unresponsive infection, pain or discomfort to patients unresponsive to trimethoprim be accounted for?

Taking a global view

This is an instructive dialogue. It is part of the process, as referred to earlier, of constructing models which describe the consequences of particular actions.

In this case it is difficult to be dogmatic. It could be argued that the GPs are there and are paid anyway, so that the additional time costs are illusory. It could also be argued that this is a true opportunity cost, and represents a lost opportunity to be doing something better and more effective with time already paid for.

Is this just an academic argument - is it real? Perhaps two ways of looking at the problem help make a decision.

Argument of extremes

The argument of extremes simply extrapolates each side of the argument to the point where they become unreal. Here, for instance, one extreme view would be that if GPs spend all their time fiddling with petty algorithms just to save a few pounds on drug costs, they'll never do anything really effective. The alternative argument might be that if fundholders manage their time *and* drug costs effectively, they will have cash to spend on other value-added services.

Argument of ranked priorities

Here one simply chooses the ranking of the priorities which one uses to make a judgement *a priori*, and then holds to the consequences. For instance, the ranking could be better for the patient, better for the doctor, better for the drug budget. That ranking would put cephalexin firmly in first place.

Further enlightenment from ***Bandolier's*** readers would be welcome.

Mindstretching meta-analyses

Three recent papers on meta-analysis merit careful examination.

Predictive ability of meta-analysis

The first concerns the predictive ability of meta-analysis, namely the ability of a meta-analysis to predict the results of trials that may be done in the future [1]. The research workers calculated relative risks for 30 meta-analyses of different interventions in perinatal medicine and compared the results with the results of the largest trial done in each intervention. Twenty-four of the 30 meta-analyses correctly predicted the direction of effect in the largest trial.

A meta-analysis demonstrating a protective effects of more than 40% from an intervention had a 60% probability of correctly predicting results of the same magnitude of the largest trial.

The authors confirm the finding that "accumulative meta-analysis can help determine when additional studies are no longer needed and approve the predictability of previous small trials", referring to the classic paper of Lau et al [2]. But they emphasised that the results of meta-analysis are influenced by the readers of the technique, "especially the way the trials are selected".

This same theme was dealt with in two leading articles in the BMJ of the same week. March 25 was a big week for meta-analysis and the press.

An effective intervention that wasn't

The reasons for the leading articles in the BMJ was that in 1993 it was argued that magnesium treatment for myocardial infarction was, on the basis of a meta-analysis, "effective, safe, simple and inexpensive". However, the negative findings of ISIS 4, the Fourth International Study of Infarct Survival, contradicted the findings of meta-analysis.

ISIS 4 was a huge trial and offers the opportunity of comparing very large trials with meta-analysis. The authors of the leading article on misleading meta-analysis emphasised a number of points about meta-analysis:-

- That more research is needed into the process of meta-analysis.
- That registers of clinical trials are essential to reduce the risk of negative trials disappearing from view. The NHS R&D Programme's project register system is designed to overcome this problem, at least for trials in the UK.
- That results of meta-analysis exclusively based on small

trials should be distrusted because "several medium-sized trials of high quality seem necessary to render results trustworthy".
- The results of meta-analysis should be subjected to careful analysis to test the robustness of the findings [3].

Too good to be true

The other leading article [4] was written by one of the authors of the meta-analysis in question. He and a colleague addressed the lessons to be learned from this changing conclusion, emphasising that there were two important lessons. The first was that a meta-analysis of small trials should not be a replacement for large, carefully conducted trials. Second was the need to be cautious of results that seemed too good to be true, and a more focused use of the lower confidence interval of risk reduction as a representation of what may be actually the clinical case - and is it useful?

Mindstretching megablast

Bandolier usually offers only one paper as a mind stretcher for busy people. These papers are so important that on this occasion we recommend several. And if you think that's it - look at reference 5.

References:

1 J Villar, G Carroli, JM Belizan. Predictive ability of meta-analyses of randomized controlled trials. Lancet 1995 345: 772-6.

2 J Lau et al. Cumulative meta-analysis of therapeutic risk for myocardial infarction. New England Journal of Medicine 1992 327: 248-54.

3 M Egger, GD Smith. Misleading meta-analysis: lessons from "an effective, safe, simple" intervention that wasn't. British Medical Journal 1995 310: 752-4.

4 S Yusuf, M Flather. Magnesium in acute myocardial infarction. British Medical Journal 1995 310: 751-2.

5 KL Woods, DB Barnett. Magnesium in acute myocardial infarction. British Medical Journal 1995 310: 1669-70.

DRUG TREATMENT OF OBSESSIVE-COMPULSIVE DISORDER (OCD)

Obsessive-compulsive disorder is a common psychiatric condition with a prevalence of up to 1% of adults, in which the patient engages in repetitive actions (compulsions, e.g. hand washing) or trains of thought (obsessions, e.g. counting rituals) which he knows are irrational but which, if he stops, lead to incapacitating anxiety.

Standard first line psychiatric treatment is either clomipramine (an older tricylic antidepressant with strong effects on the neurotransmitter serotonin) or one of the newer specific serotonin re-uptake inhibitors (SSRIs). A recent meta-analysis [1] attempts a systematic review of the evidence for this approach.

Systematic review of RCTs

Since OCD is a chronic, relapsing and remitting condition, where treatment effects are generally modest, the review is rightly restricted to randomised controlled trials. The authors describe a strategy of computer and manual searching to identify as many as possible, and found as many as 53.

Thirty-six were admitted into the analysis, and the reason for each exclusion is described clearly (e.g. "diagnostic criteria not strictly enforced" (!)).

The authors tried to obtain any necessary original data, for calculation of effect size. The statistical procedure used was Hedges 'g' (an effect size measure), unfamiliar to most colleagues consulted.

Results

The result of the meta-analysis is expressed in an unusual though logical format, as "increase in improvement rate over placebo", given as 61% for clomipramine and 22-28% for SSRIs.

Although the techniques used are difficult for the non-statistician, the results seem broadly supported by scanning the helpful tables summarising each study.

The review addresses publication bias (negative studies selectively unpublished: the "file-drawer" problem), by statistically suggesting the number of negative studies which would be needed to "cancel out" the conclusions of the review. Another possible source of bias, not considered, relates to methodological quality, particularly randomisation: rigorous randomisation is associated with lower treatment effects. In 60% of studies, results analysed excluded drop-outs (i.e. no "intention to treat") analysis: this is a possible source of bias. The review could have been made more rigorous by arbitrarily assigning negative outcomes to non-completers.

Conclusion

This is a good systematic review, and does a great service in identifying 53 RCTs.

Although repeat analysis using different statistical procedures and addressing the above biases would be helpful, the authors seem justified in concluding cautiously that:

1 Antidepressants are effective in the short term treatment of OCD.
2 Clomipramine / SSRIs are more effective than non-serotonergic drugs.
3 Concomitant depression is not necessary for effectiveness.

Practice Points

Clomipramine should be first line treatment in OCD as it is effective, well established and cheap.

SSRIs should be reserved for those with side effects or non-responders, as they are more expensive and newer. There was also a trend toward their being less effective than clomipramine.

Behavioural therapy and other psychological treatments are less readily available and more expensive in the short term. They may be tried when drugs have failed, and also in chronic cases, where the evidence for drug effectiveness is much weaker.

David Gill
Senior Registrar in Psychiatry, Oxford

Reference:

M Piccinelli, S Pini, C Bellantuono, G Wilkinson. Efficacy of drug treatment in obsessive-compulsive disorder: A meta-analytic review. British Journal of Psychiatry 1995 166: 424-43.

NOTHING BUT THE TRUTH

Pharmaceutical representatives provide information to doctors and others about some of the most important remedies used in medicine. Doctors may change their prescribing advice based on such information, and, though the way medicines are promoted is certainly changing, information from this source probably still represents a significant influence on why doctors do things.

How do we know they tell the truth?

This is exactly what researchers at San Diego set out to do. Lunch time training conferences were held as part of the normal teaching programme - with pharmaceutical representatives occasionally giving brief presentations about their products. Talks were regularly tape recorded.

Recordings of 13 talks given by pharmaceutical company representatives were transcribed by a pharmacist who attended the meeting and statements were analysed - 106 were eligible for analysis.

For a statement to be classified as incorrect it had to meet all of three criteria:-

1 It clearly contradicted prescribing information in the Physicians' Desk Reference or literature quoted or handed out by the representative.

2 A pharmacist and doctor independently assessed the statement as incorrect.

3 A search of reference books, brochures and MEDLINE provided no support for the statement.

Statements were classified as favourable if they encouraged prescribing of the medicine, unfavourable if they discouraged prescribing or neutral if the statement was neither clearly favourable nor unfavourable.

Results

Presentations averaged 2.4 minutes (from 30 seconds to 12 minutes). In all there were 106 statements, of which 12 were inaccurate. All were favourable to the medicine being promoted.

There were 15 statements about competitors' medicines. All were accurate but none were favourable.

Comment

Is this a surprise? Perhaps not.

Is it a hard judgement? Well, the criteria for a statement to be inaccurate were harsh - so these were not trivial inaccuracies. The inaccurate statements are given in the paper - so you could judge how important they were by reading them yourself.

What would the inaccuracy rate be for academic presentation? Don't know, though these do last more than 2.4 minutes on average, and most people have sat through at least one lecture they thought was *complete* drivel.

Analysis of 106 statements about medicines

Accuracy of statement	Favourable	Neutral	Unfavourable
Inaccurate about promoted drug	12	0	0
Accurate about promoted drug	39	25	15
Inaccurate about other drug	0	0	0
Accurate about other drug	0	6	9

Ultimately doctors themselves are responsible for judging the reliability of the medical information they use, but this paper also shows that the provision of information from pharmaceutical company representatives formed a significant portion of their information base.

Reference:

MG Ziegler, P Lew, BC Singer. The accuracy of drug information from pharmaceutical sales representatives. Journal of the American Medical Association 1995 273: 1296-8.

SWOTS' CORNER
NNTS AND CONFIDENCE INTERVALS

Why Bother?

NNT values without confidence intervals may be better than nothing, but they do not tell you how likely the values, or 'point estimates', are to be true. A p value tells you that a result is seldom likely to occur by chance (less than 1 or 5% of the time). A confidence interval can tell you where the true value is most likely to be (more than 90 or 95% of the time). "You can be 95% certain that the truth is somewhere inside a 95% confidence interval". [1]

Calculating NNT

$$NNT = \frac{1}{\left(\frac{Ia}{Ta}\right) - \left(\frac{Ic}{Tc}\right)}$$

	Active	Control
Total	Ta	Tc
Improved	Ia	Ic

The NNT is the reciprocal of the absolute risk reduction.

Calculating Confidence Intervals

The pukka method is to "invert and exchange the limits of a 95% CI for the ARR" [2]. The calculation using the confidence interval derivation for proportions is to be found in reference 3 and at the bottom of the page.

When not to

If the odds ratio for the result is not significant (lower odds ratio confidence interval ≤ 1), then it is unwise to bother with the confidence intervals for the NNT - see Mulrow's excellent paper [4] featured in ***Bandolier*** 15.

References:

1. Sackett DL, Haynes RB, Guyatt GH, Tugwell P. Clinical Epidemiology: a basic science for clinical medicine. Boston: Little, Brown, 1991.
2. Cook RJ, Sackett DL. The number needed to treat: a clinically useful measure of treatment effect. British Medical Journal 1995; 310: 452-4.
3. Gardner MJ, Altman DG. Statistics with confidence. London: British Medical Journal, 1989.
4. CD Mulrow, JA Cornell, CR Herren, A Kadri, L Farnett, C Aguilar. Hypertension in the elderly. Implications and generalizability of randomized controlled trials. Journal of the American Medical Association 1994 272: 1932-8.

STOCKING FILLER

Systematic Reviews, Edited by Iain Chalmers and Doug Altman. 1995. BMJ Publishing Group. 117pp. £14.95.
ISBN 0-7279-09054-5.

This book won't tell you everything about systematic reviews, but it will really get you up to speed. The eight chapters in the book are based on papers presented at a joint BMJ / UK Cochrane Centre meeting held in 1993. Perhaps because of this the chapters often come over very fresh and individualistic.

Some are fun. Paul Knipschild gives some very personal examples of systematic reviews and the fun and games that ensue. Hans Eysenck challenges the basis of meta-analysis, and points to many of the problems that can occur.

Others are a bit more dry (perhaps the nature of the beast) because good and reliable systematic reviews have to be based on good and reliable methods - so quality control in its widest meaning can tend to dominate the excitement of mining pearls of wisdom. Heterogeneity, as one example, is not the most thrilling of subjects.

This book is more than a "new readers start here" primer. It is a useful reminder for those conducting systematic reviews of the basic principles and ideas from whence it all sprang. A really useful book - needed on the bookshelf.

$$NNT\ CIs = 1/\left((Ia/Ta) - (Ic/Tc)) \pm \left(1.96 * \sqrt{(((Ia/Ta)*(1-(Ia/Ta))/Ta) + ((Ic/Tc)*(1-(Ic/Tc))/Tc)}\right)\right)$$